Rivaroxaban for ACS sNDA 202439/S-002

Cardiovascular and Renal Drugs Advisory Committee Meeting

January 16, 2014

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Outline -1

- Regulatory history
- Review issues in previous submissions
  - Subjects with incomplete follow-up
  - Analysis datasets
    - ITT vs OT+30d
    - Both strata vs stratum 2 only
    - Pooling results from both doses
    - Exclusion of 3 investigative sites
    - Subgroup analyses

Outline -2

- Adequacy of support for single trial approval
- Other issues
  - Bleeding
  - Rivaroxaban (riva) does not address unmet medical need
- Support for limited duration of treatment

Regulatory History
sNDA 202439/S-002

Dec 29 2011	sNDA submitted seeking approval to market rivaroxaban 2.5 mg bid to reduce the risk of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS)
May 23 2012	Cardiovascular and Renal Drugs Advisory Committee meeting. Committee votes 4 for - 6 against - 1 abstain
Jun 21 2012	Division of Cardiovascular and Renal Products (DCaRP) declines to approve sNDA indicating the strength of evidence was inadequate for a single trial approval and the outcomes at the end of the trial were unknown for an excessive number of subjects
Aug 29 2012	Complete response for sNDA submitted, which included vital status on 843 of the 1338 subjects whose vital status was unknown at the end of ATLAS

Regulatory History -2

Mar 4 2013	DCaRP again declines to approve sNDA for similar reasons as before
May 13 2013	Formal dispute resolution submitted requesting that the Office of Drug Evaluation 1 (ODE-1) approve the sNDA
Jun 13 2013	ODE-1 declines to direct DCaRP to approve sNDA indicating the p-value for the primary analysis was insufficiently low for a single trial approval
Aug 12 2013	2nd complete response for sNDA submitted seeking a new indication limiting the suggested duration of treatment to 90 days

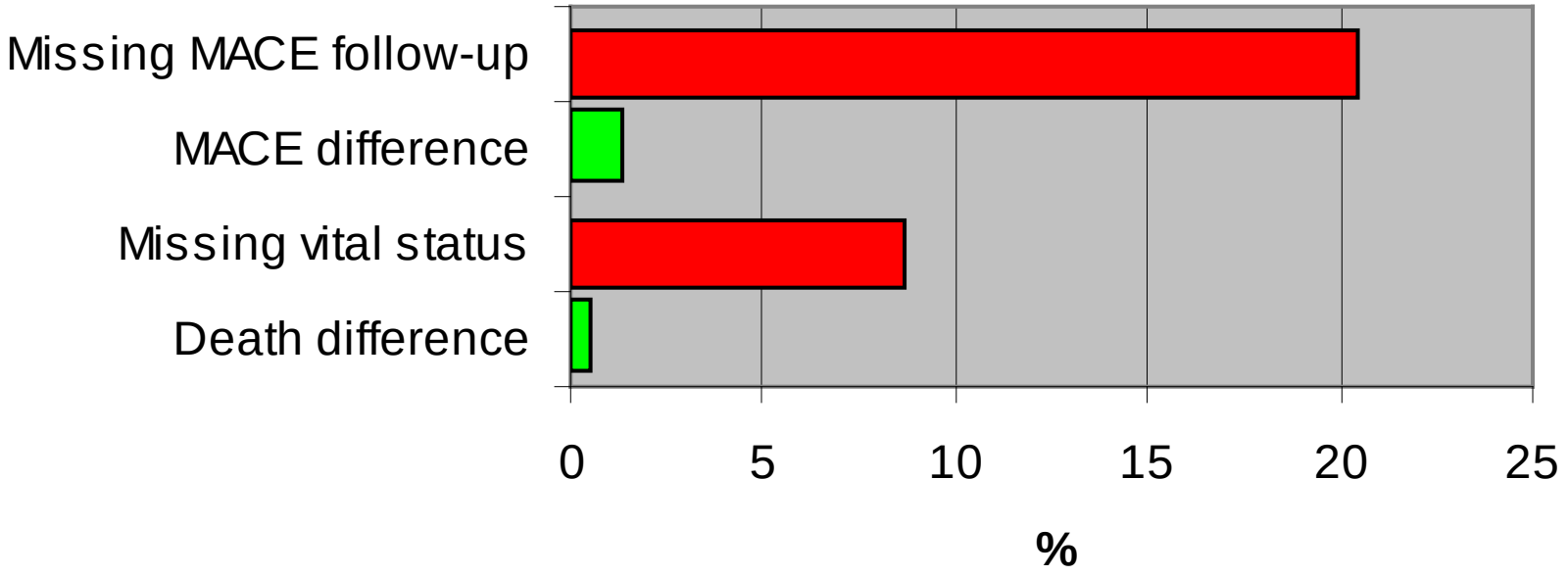
Incomplete Follow-up

- Incomplete follow-up refers to not knowing the status of any event that is part of the primary endpoint at the conclusion of the trial
- 1509 subjects (~ 10%) in ATLAS had incomplete follow-up using the applicant's data
- 799 subjects had incomplete follow-up if the observation period is limited to 30 days after early discontinuation (OT+30d)
- Applicant determined vital status of 843 of 1338 subjects for whom vital status was unknown at the end of the trial

Missing Follow-up vs. Endpoint Differences

(Before new f/u)

Both rivaroxaban doses vs. placebo, ITT



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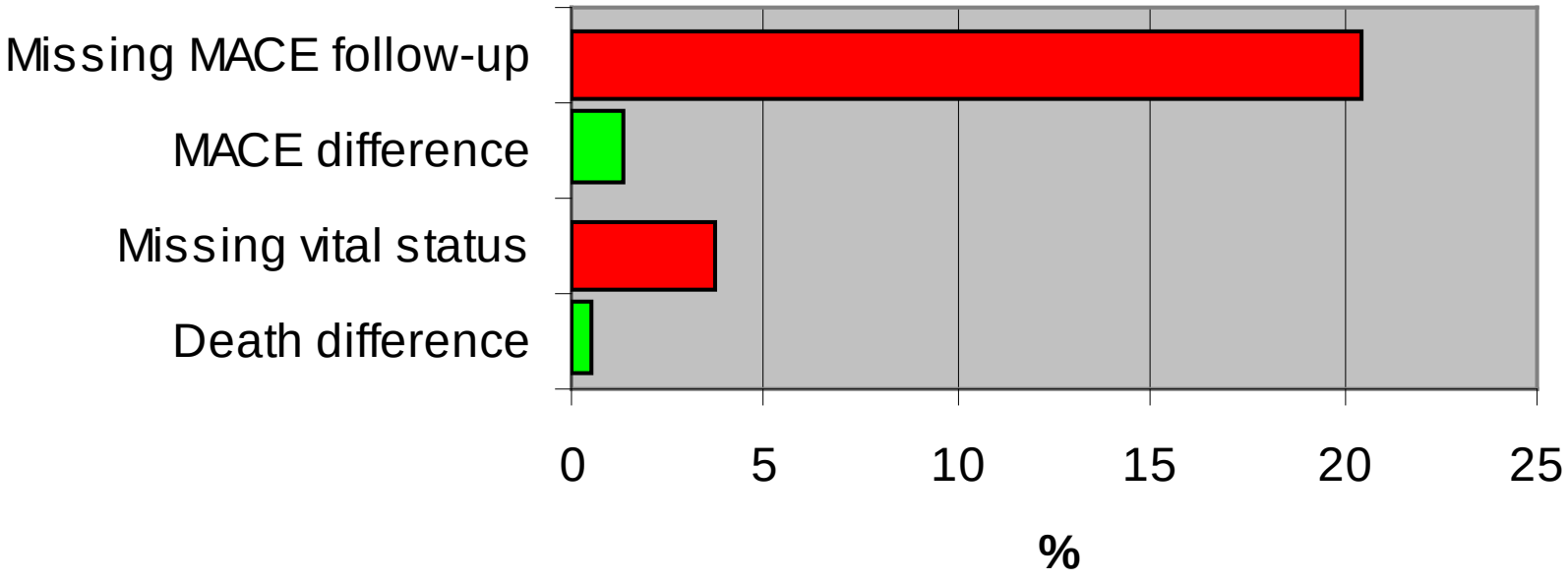


Not All Patients Missing Vital Status Were Followed-up

- 24% of patients missing vital status had no additional follow-up
  - 26% placebo
  - 39% 2.5 mg
  - 35% 5.0 mg
- 18% of the follow-up attempts failed
  - Optimistic because of failed death registry searches

New f/up Not Uniform by Treatment Arm

Rates of TIMI minor/major bleeds by further follow-up status

Treatment	Further follow-up status		
	Incomplete	Complete	Not done
Placebo	0%	1.1%	1.2%
Riva 2.5 mg	0%	1.5%	2.3%
Riva 5 mg	1.5%	3.1%	4.3%

Effect of Ascertaining Vital Status on Additional Subjects

- 22 additional riva subjects and 9 additional placebo subjects in stratum 2 were found to have died during ATLAS
- Increases p-value for ITT analysis of time to death from 0.045 to 0.076

Effect of Unequal Incomplete Follow-up

All-cause mortality (ITT) using all data available

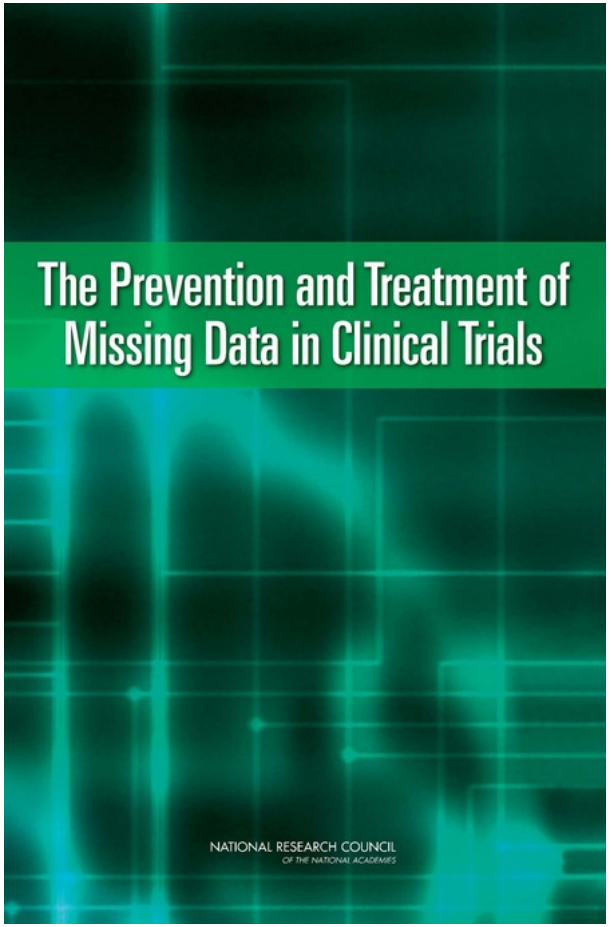
Stratum 2	N	Deaths	Vital status unknown	HR (95% CI)	p-value
Placebo	4821	183	124		
Rivaroxaban	9652	309	340	**0.85 (0.71, 1.02)**	**0.076**

- The proportion of riva subjects missing vital status is greater than placebo subjects
- True in other datasets and other endpoints such as OT+30d and the composite of CV death, MI & stroke

All-cause Mortality Using Imputed Data

Imputed mortality rate	Mortality rates applied (placebo vs riva)	Additional deaths imputed	HR (95% CI)	Nominal p-value
No imputation	3.80% vs. 3.20%	0	0.85 (0.71, 1.02)	**0.076**
Observed rate for each treatment group	3.80% vs. 3.20%	5 vs. 11	0.85 (0.71, 1.02)	**0.087**
Pooled rate for all subjects	3.40% vs. 3.40%	5 vs. 12	0.86 (0.72, 1.03)	**0.093**
Placebo rate	3.80% vs. 3.80%	5 vs. 13	0.86 (0.72, 1.03)	**0.100**

The National Research Council's Panel on Handling Missing Data



"There is no 'foolproof' way to analyze data subject to substantial amounts of missing data; that is, no method recovers the robustness and unbiasedness of estimates derived from randomized allocation of treatments."

The Panel's Recommendations

- "The first set of recommendations emphasizes the role of design and trial conduct to limit the amount and impact of missing data."
- "Recommendation 3: Trial sponsors should continue to collect information on key outcomes on participants who discontinue their protocol specified intervention in the course of the study..."

Analysis Datasets: ITT vs. OT+30d

- FDA agreed that the primary analysis could be of events that occurred while subjects were taking study drug + 30 days after early discontinuation (OT+30d)
- FDA did so in part because the applicant stated "all efforts will be expended in capturing the status of all subjects at the end of the study."

Analysis Datasets: ITT vs. OT+30d -2

- Data needed for reliable ITT analyses are not available due to incomplete follow-up
- Although analyzing only OT+30d data may not have been optimal, FDA believed these data were capable of providing information useful for regulatory decision making

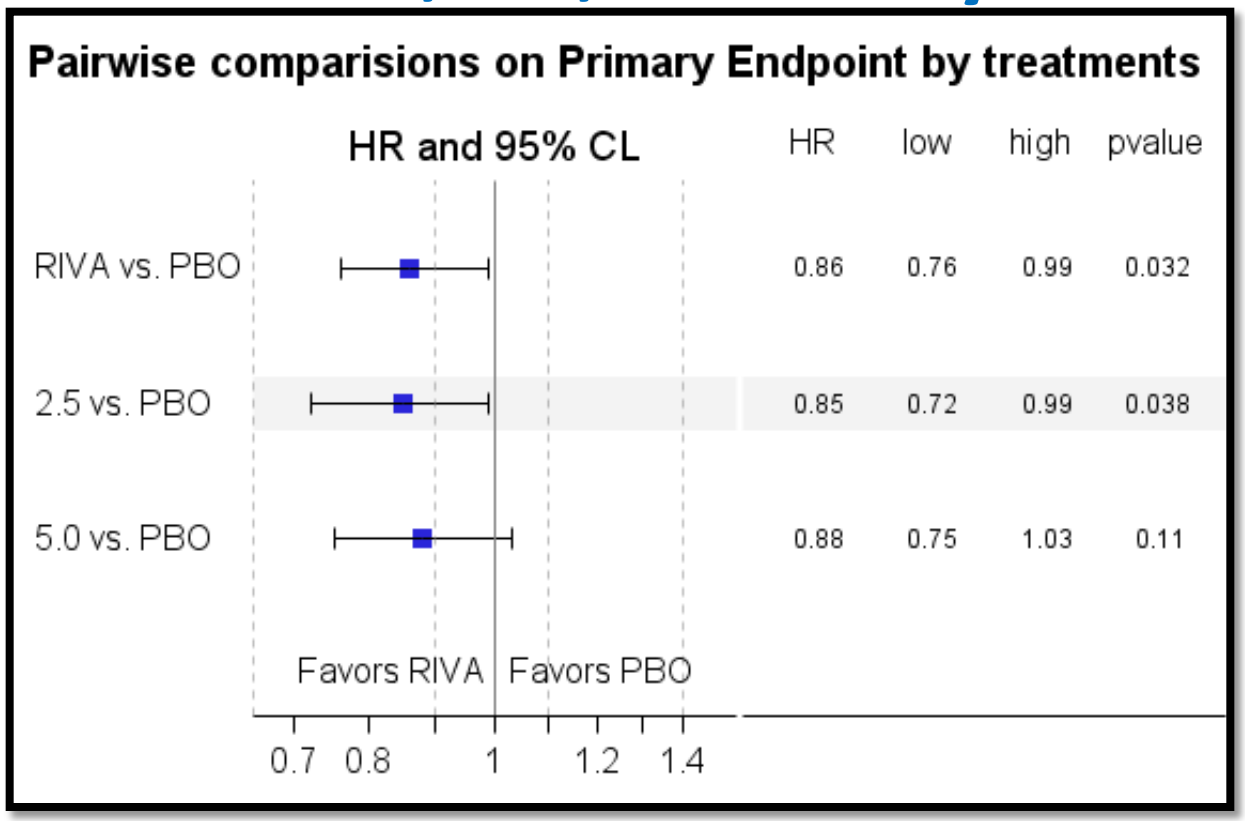
Analysis Datasets: Both Strata vs Stratum 2 only

- FDA requested and the applicant agreed that for US regulatory purposes, analysis of the primary endpoint had to be successful in stratum 2
- ATLAS was not designed to provide evidence that rivaroxaban should be administered in lieu of a thienopyridine - that would require a direct comparison

Analysis Datasets: Both Doses vs Each Dose Separately

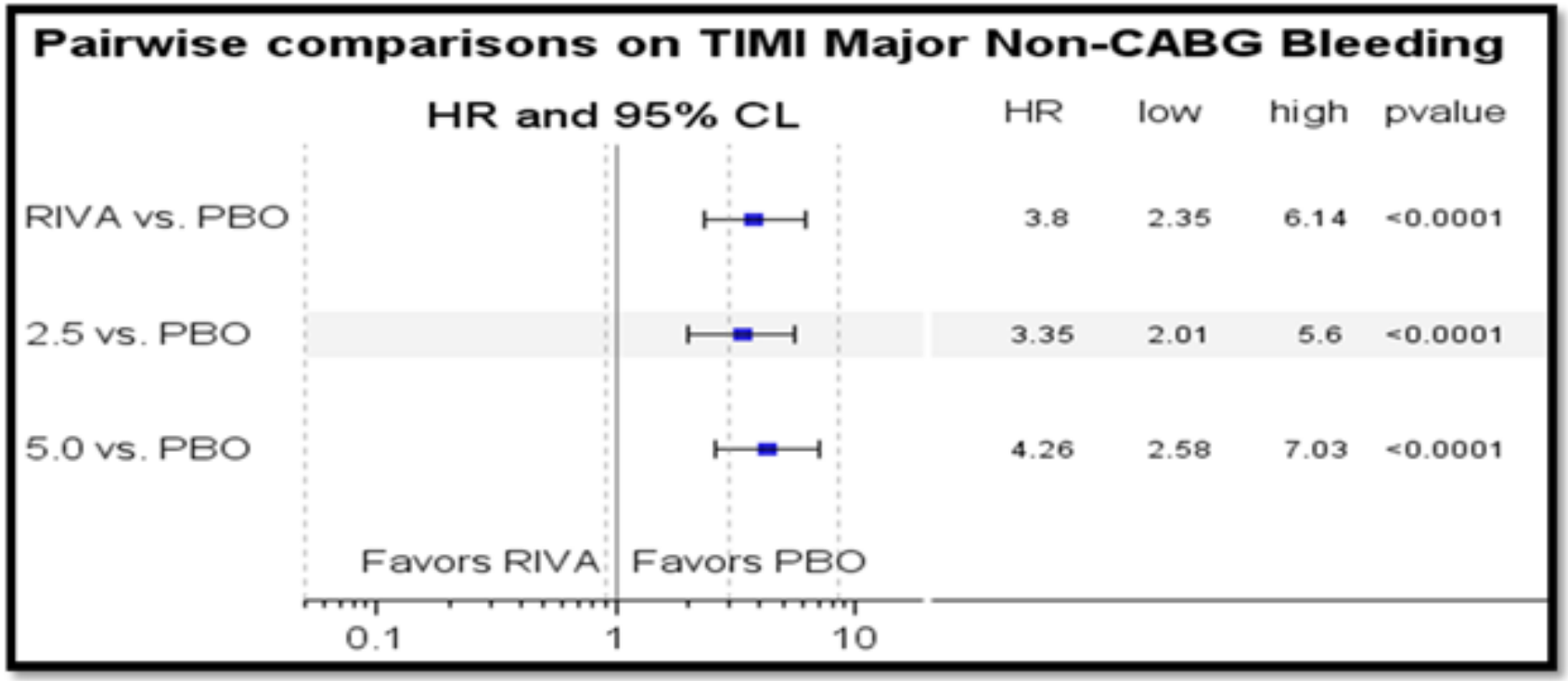
- FDA and the applicant agreed that analysis of the primary endpoint would be a comparison of the pooled results of both doses of rivaroxaban vs. placebo
- Pooling results of doses does not increase the probability of falsely concluding the drug is effective
- Doses were similar enough that results were not expected to differ much

Analysis of Time to CV Death, MI, Stroke by Dose



- Nominal p-value comparing the 2.5 mg dose to the 5.0 mg dose is 0.63 (95% CI 0.82, 1.13)

Analysis of Time to TIMI Major Non-CABG Bleed by Dose



- Nominal p-value comparing the 2.5 mg dose to the 5 mg dose is 0.16 (95% CI 0.56, 1.09)

Analysis Datasets: Both Doses vs Each Dose Separately - Conclusion

- Pooling the results of both doses for the primary efficacy analysis is acceptable because the efficacy and safety of both doses are similar
- There is a trend toward less bleeding with the 2.5 mg bid dose

Analysis Datasets: Excluding Data from 3 Investigative Sites

- DCaRP routinely advises sponsors not to make changes to a SAP after significant information has accumulated
- If late changes are made, then the effect of the changes need to be made explicit by providing analyses with and without them

Analysis Datasets: Excluding Data from 3 Investigative Sites

- In the SAP finalized one week prior to completion of ATLAS, data from three investigative sites were excluded from efficacy analyses for GCP violations
- FDA reviewers concluded that the subjects reported as having efficacy events
  - existed,
  - met entry criteria,
  - were randomized and received study drug, and
  - the events reported occurred.

Analysis Datasets: Excluding Data from 3 Investigative Sites

- Generally if late changes are made to a SAP, DCaRP will use the most conservative estimate of the drug effect
- At these three sites the results were unfavorable to rivaroxaban
- Including the data modestly increases the p-value for the primary efficacy analysis from 0.024 to 0.032.

Analysis Datasets: Subgroup Analyses

- Generally, subgroup analyses not contained within a hierarchical plan to preserve alpha may be supportive but are not considered to improve the persuasiveness of the overall results

Adequacy of Support for Single Trial Approval -1

- A single trial providing "highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would (be) difficult to conduct on ethical grounds" may be adequate support for approval
- In interpreting what constitutes "statistically strong evidence" DCaRP has considered what p-value would be considered such strong evidence of a therapeutic effect that another study could not be ethically conducted

Adequacy of Support for Single Trial Approval -2

- Generally, DCaRP has advised sponsors that a single well-designed and well-conducted trial may be sufficient for approval if it demonstrates either:
  - a reduction in all-cause mortality at a p-value < 0.05 or
  - a reduction in irreversible morbidity and mortality (such as CV death, MI, and stroke) at a p-value < 0.01
- DCaRP informed the applicant before ATLAS was initiated that because approval would be based on results from a single study "it would have to be adequately persuasive, i.e., at an alpha level much less than 0.05."

Time to Composite of CV Death, MI, & Stroke
(stratum 2) (OT+30d) (including 3 Indian sites)

	N	Incomplete f/up	Events	Annualized event rate	HR (95% CI)	p-value
Placebo	4821	217	342	6.75		
Riva	9652	518	583	5.88	**0.86 (0.76, 0.99)**	**0.032**
2.5 mg	4825	257	288	5.75	0.85 (0.72, 0.99)	0.038
5.0 mg	4827	261	295	6.02	0.88 (0.75, 1.03)	0.11

Adequacy of Support for Single Trial Approval -3

- DCaRP concluded that a p-value of 0.032 (or 0.024) was not low enough to support approval
- DCaRP had additional concerns about conduct and design of ATLAS
  - —Incomplete follow-up
  - —Lack of testing for CYP2C19 variants and use of PPIs that impair conversion of clopidogrel to its active metabolite

Lack of Independent Substantiation

- Results in both doses were similar but p-value for 5 mg dose is 0.11
- Results in subjects who underwent PCI for index event and those who did not undergo PCI were expected to be similar but were not
- Results in stratum 2 in dose finding study (TIMI 46) were not supportive [HR 1.03 (95% CI 0.73, 1.45) for primary endpoint (death, MI, stroke, or severe ischemia requiring revascularization)]

Time to Composite of CV Death, MI, & Stroke: PCI vs No PCI

(stratum 2) (OT+30d) (including 3 Indian sites)

	N	Events	Incomplete f/up	Event rate (/yr)	HR (95% CI)	p-value
No PCI for index event						
Placebo	1743	177	79	9.77	-----	------
Riva	3456	289	197	7.98	0.82 (0.68, 0.99)	**0.036**
PCI for index event						
Placebo	3078	165	138	5.07	------	-----
Riva	6195	294	321	4.68	0.91 (0.75, 1.10)	**0.32**

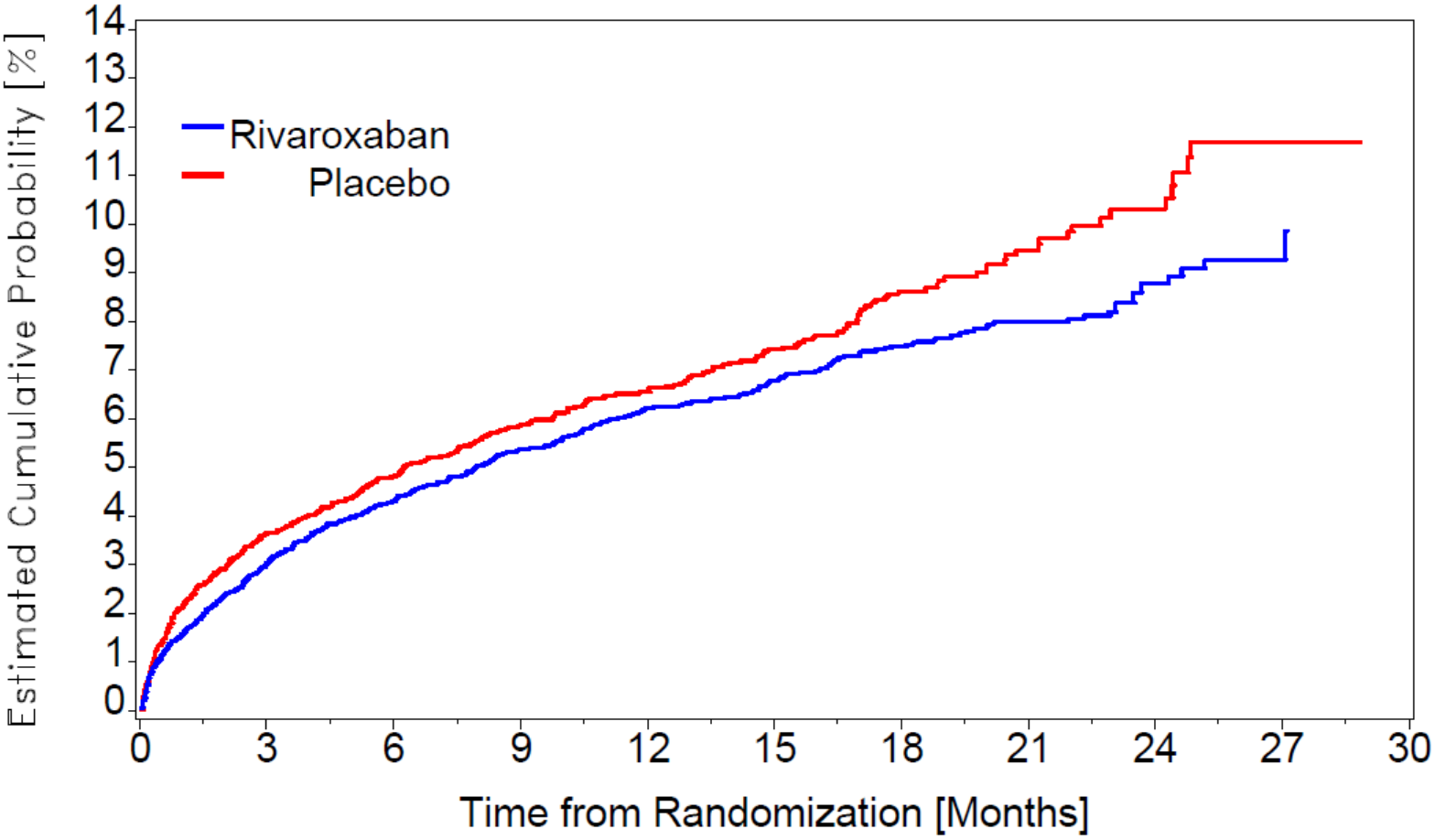
Other Issues Affecting Approvability

- Rivaroxaban resulted in ~ 1% absolute increase of TIMI major non-CABG bleeding/yr
- Rivaroxaban does not address an unmet medical need
  - If approved, the label will advise against use with ticagrelor and prasugrel because of the risk of bleeding
  - So if approved rivaroxaban + clopidogrel will be an alternative not demonstrated to be better than ticagrelor and prasugrel

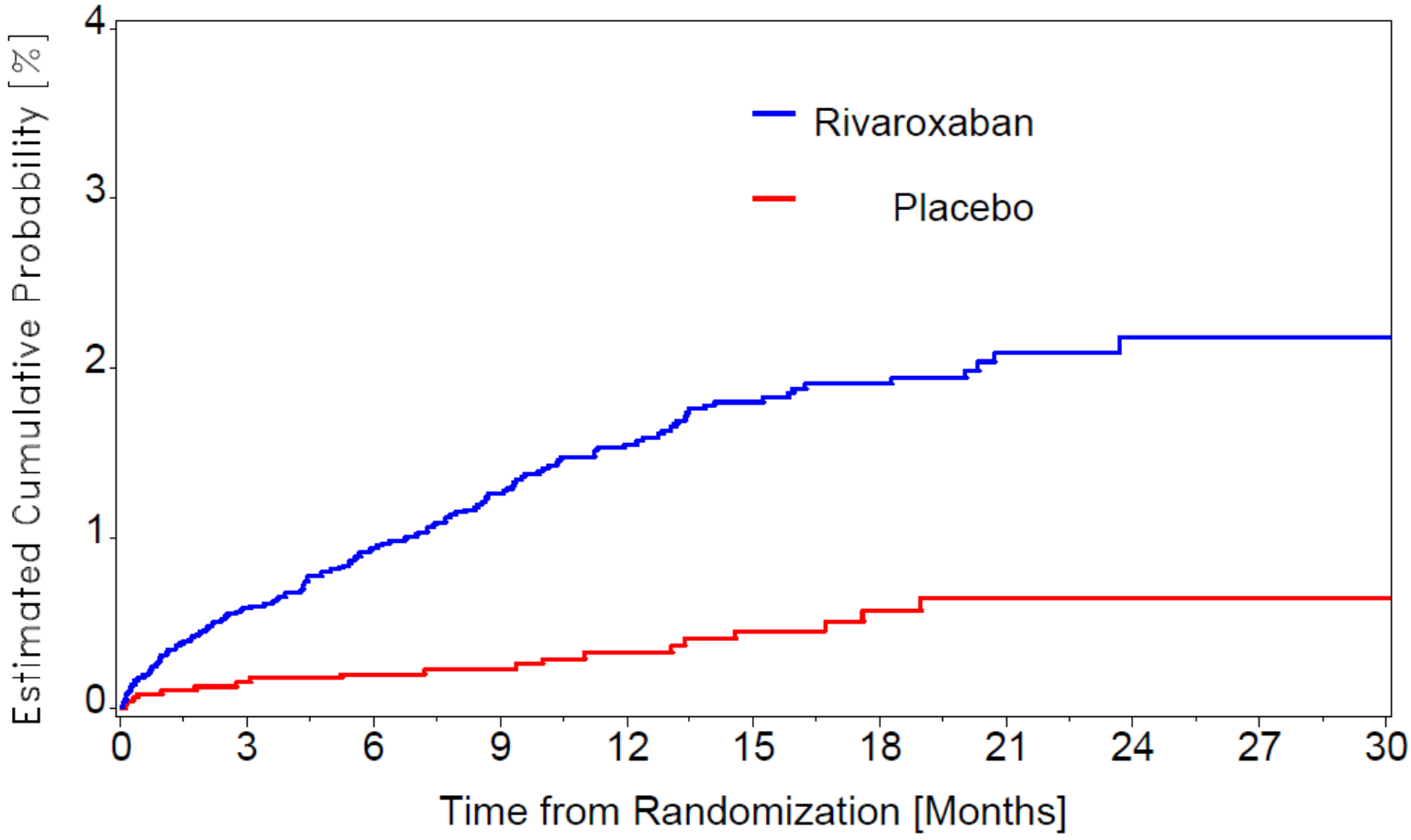
Support for Limited Duration of Treatment

- FDA has now declined to approve rivaroxaban for chronic therapy after ACS on three separate occasions
- The applicant is currently seeking approval to market rivaroxaban with a suggested duration of use after ACS limited to 90 days
- Does limiting the duration of treatment strengthen the evidence enough to support approval?

Kaplan-Meier Estimate of Time to First CV Death/MI/Stroke (stratum 2) (OT+30d)



Kaplan-Meier Estimate of Time to First TIMI Major Non-CABG Bleed (stratum 2)



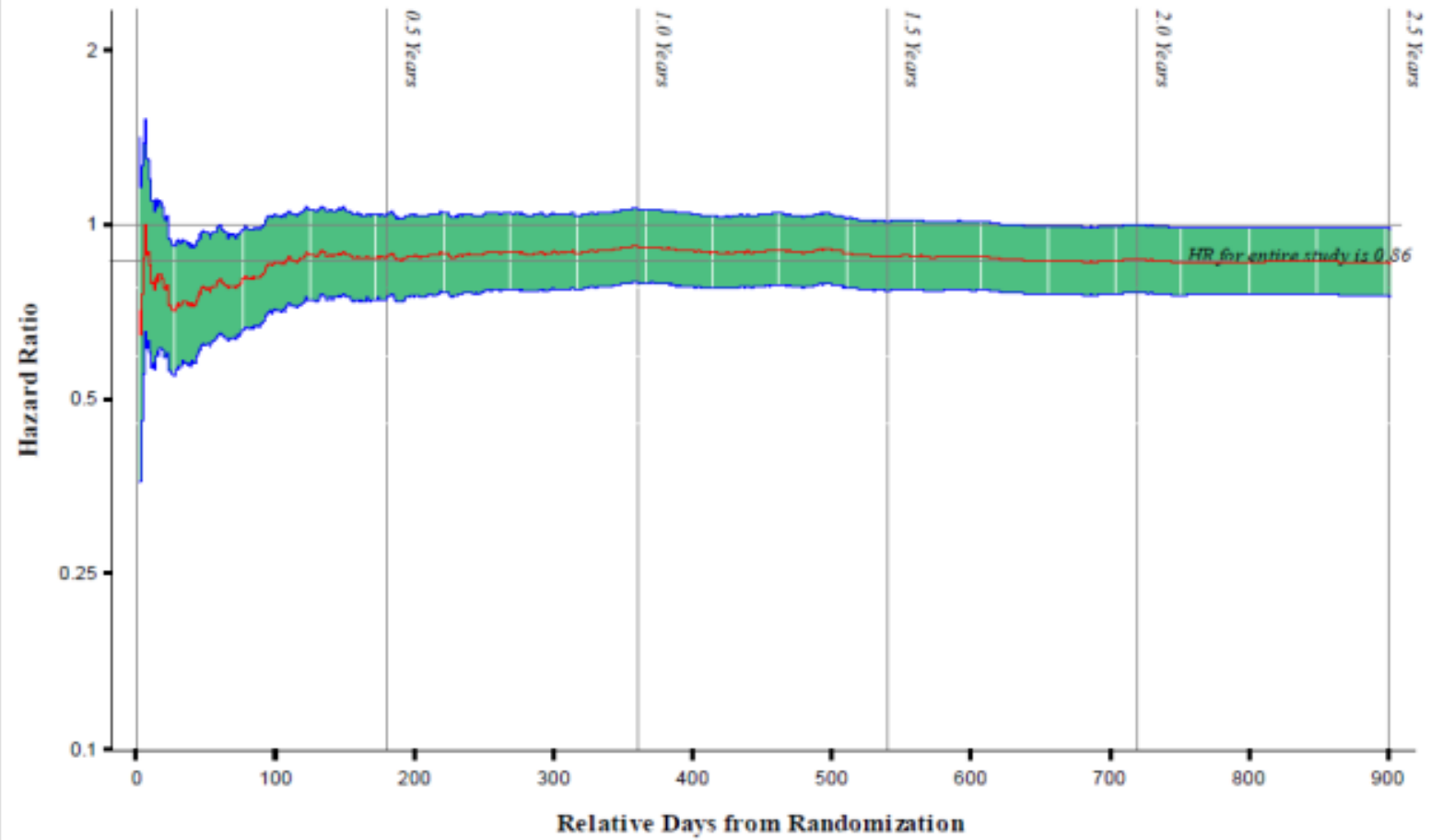
Difficulties in Analyses Supporting Limited Duration of Treatment

- Difficulties of *post hoc* analyses of these data long after unblinding
  - Not clear how to limit the probability of a spurious finding being accepted as true
  - Inherently involves examining multiple timepoints, which may also increase the risk of accepting a spurious finding as true
  - Impossible to know whether analyses were selected with knowledge of the data to get the desired results

Cumulative Occurrence of Primary Efficacy Endpoint Events (CV Death, MI, Stroke)

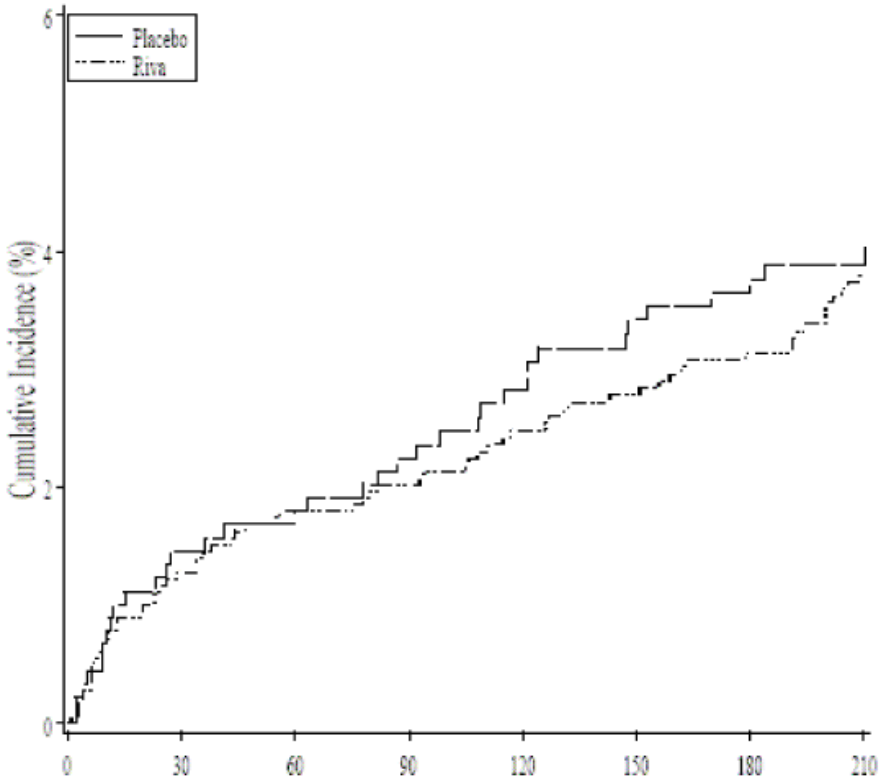
Stratum 2 OT+30d	**Placebo** (N=4821)		**Rivaroxaban** (N=9652)		
Time	Events	Incomplete f/up	Events	Incomplete f/up	HR (95% CI)
30 days	104	75	151	185	0.72 (0.56, 0.93)
60 days	138	114	223	275	0.81 (0.65, 1.00)
90 days	171	129	281	311	0.82 (0.68, 0.99)
120 days	186	153	327	354	0.86 (0.76, 1.05)
180 days	219	167	385	390	0.88 (0.75, 1.04)
Overall	342	217	583	518	0.86 (0.76, 0.99)

Hazard Ratio and 95% CI for CV Death/MI/Stroke Over Time



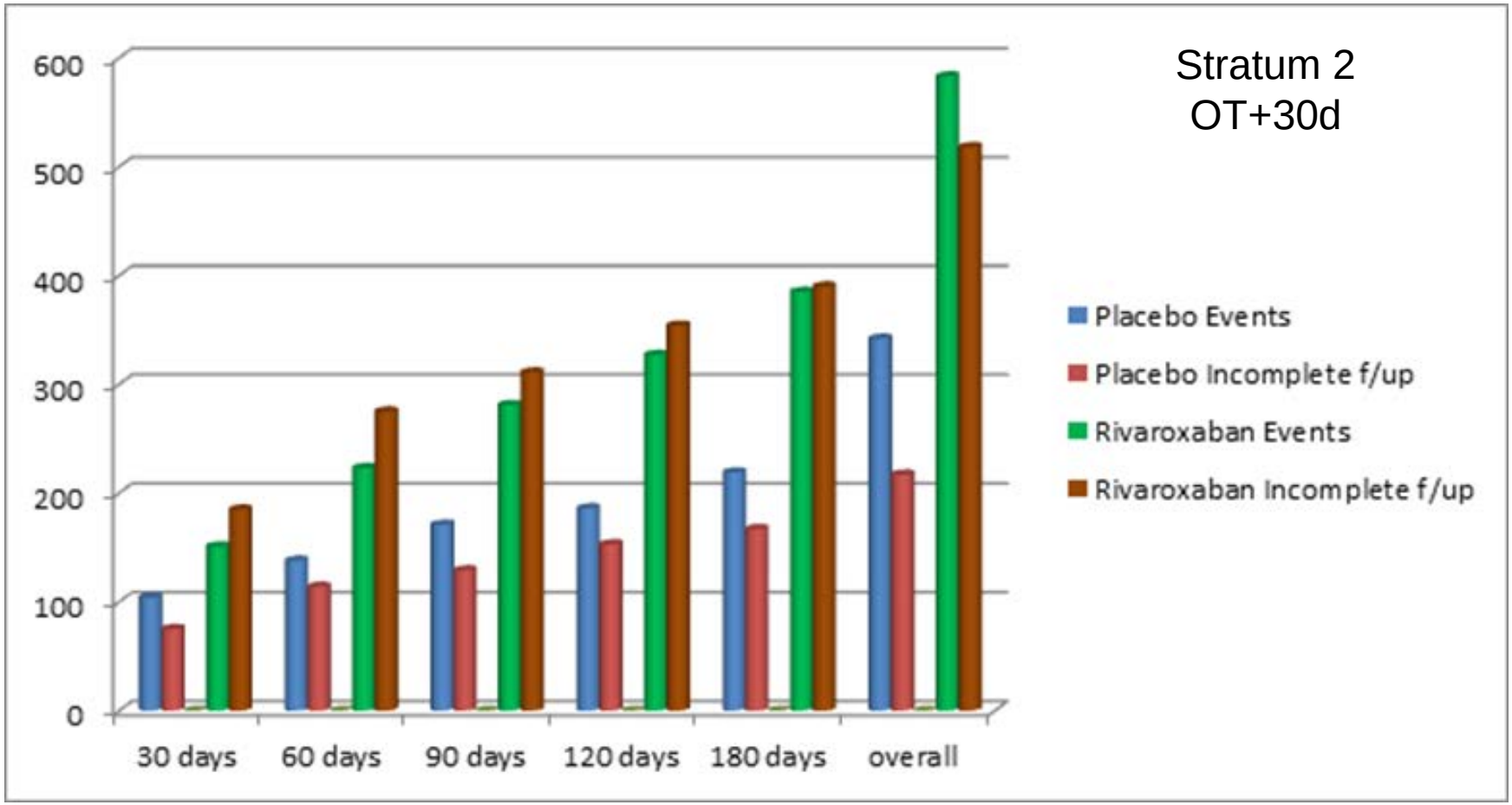
Note: Scale of Y axis was based on log transformation of the ratio. Tick labels of Y axis are in the original ratio scale.

Kaplan-Meier Estimate of Time to First Death/MI/Stroke (stratum 2 - All Doses Combined) in TIMI-46



No. Subjects at Risk								
Placebo	907	879	866	853	835	824	814	634
Riva	1823	1762	1720	1700	1671	1648	1624	1295

Number of Efficacy Events vs Incomplete Follow-up Over Time



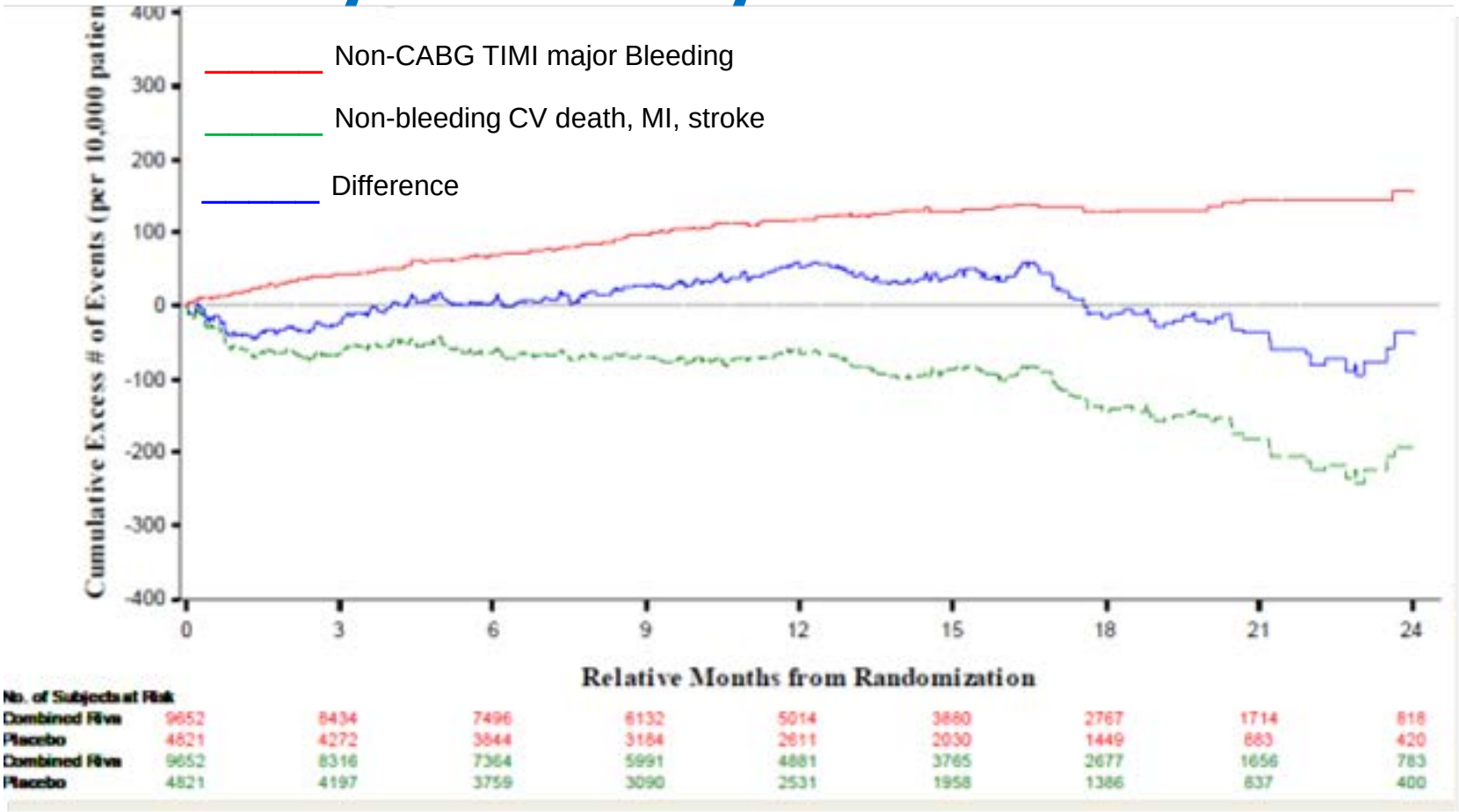
Cumulative Occurrence of Primary Safety Endpoint (TIMI Major Non-CABG Bleeding)

Stratum 2 OT+2d	**Placebo** (N=4821)	**Rivaroxaban** (N=9652)	
Time	Events	Events	HR (95% CI)
30 days	5	29	2.90 (1.13, 7.51)
60 days	6	42	3.52 (1.50, 8.27)
90 days	7	53	3.81 (1.73, 8.38)
120 days	8	60	3.78 (1.81, 7.90)
180 days	9	81	4.55 (2.29, 9.06)
Overall	19	141	3.80 (2.35, 6.14)

Proportion of Total Bleeding and Efficacy Events Over Time

	Placebo (N=4821)				Rivaroxaban (N=9652)			
Time	Bleeding events	n bleed / n total	Efficacy events	n efficacy / n total	Bleeding events	n bleed / n total	Efficacy events	n efficacy / n total
30 days	5	26%	104	30%	29	21%	151	26%
60 days	6	32%	138	40%	42	30%	223	38%
90 days	7	37%	171	50%	53	38%	281	48%
120 days	8	42%	186	54%	60	43%	327	56%
180 days	9	47%	219	64%	81	57%	385	66%
Overall	19		342		141		583	

Difference Between Occurrence of Efficacy and Safety Events Over Time



Support for Limited Duration of Treatment - Conclusions

- Examining results at earlier time points does not strengthen the evidence provided by the overall trial results.
  - type-1 error is not limited
  - Does not conclusively demonstrate that the effect of rivaroxaban as measured by the relative risk reduction is greater earlier than later
  - In relation to the occurrence of efficacy events, incomplete follow-up is not less early

Support for Limited Duration of Treatment - Conclusions

- Examining results at earlier time points does not strengthen the evidence provided by the overall trial results.
  - In relation to the occurrence of efficacy events, the risk of bleeding is not notably less early
  - No obvious method for deciding which time point to choose

Back-up Slides

Rivaroxaban for Stent Thrombosis -1

1. Stent thrombosis was not a prespecified endpoint in the ATLAS protocol or the statistical analysis plan
2. The applicant did not prespecify whether ARC definite, probable, or possible stent thrombosis or ARC definite or probable stent thrombosis was the key analysis
3. The applicant did not prespecify whether the key analysis would include all stents, stents placed at the index event only, stents placed prior to or at randomization, or stents placed during the course of the study
4. Therefore all stent thrombosis results should be considered to be exploratory in nature

Rivaroxaban for Stent Thrombosis -2

- A *post hoc* informal exploratory analysis provides minimal, if any, support for approval
- If approved for ACS, could be described in the label in order to provide "best possible description" of the trial results
- The total number of events is small (~ 120 definite/probable) and the effect of clopidogrel in preventing stent thrombosis is large so use of PPIs or genotypic variation that impairs the action of clopidogrel in even a small numbers of subjects could be important

ENGAGE AF –TIMI 48

NEJM 2013; 369:2093-2104

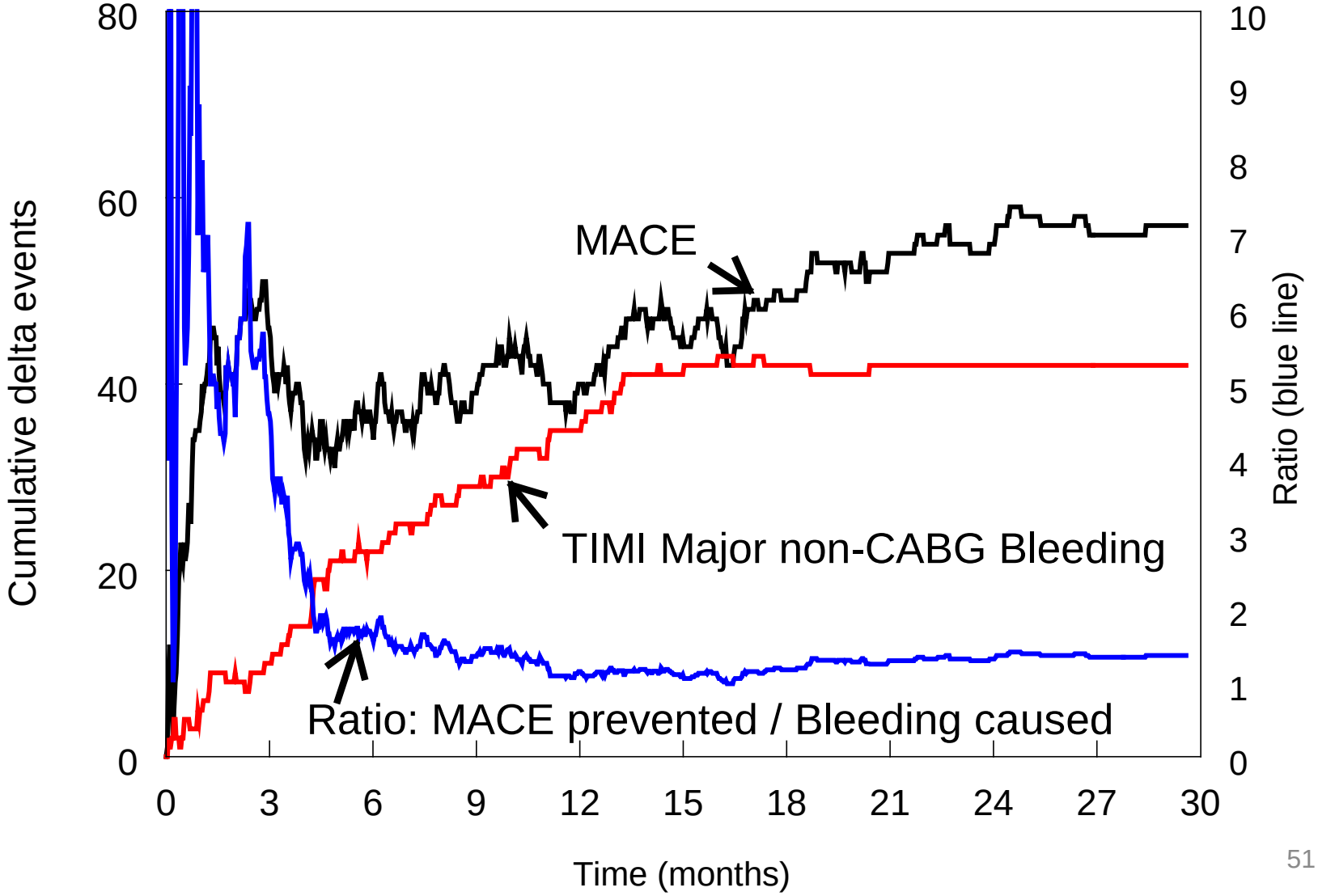
- Randomized, double-blind, double-dummy trial comparing two regimens of edoxaban with warfarin in 21,105 patients with atrial fibrillation (median follow-up, 2.8 years).
- Conducted at 1393 centers in 46 countries beginning in November 19, 2008
- “Complete information on the primary end point was ascertained for 99.5% of the total 56,346 patient-years of potential follow-up. One patient was lost to follow-up, and 244 patients withdrew consent to follow-up; 182 of these patients had no known primary-end-point event and were not known to be dead.”

Time to Composite of CV Death, MI, & Stroke
(Stratum 1) (OT+30d) (including 3 Indian sites)

	N	Events	HR (95% CI)	Nominal p-value
Placebo	355	36		
Rivaroxaban	698	51	0.69 (0.45, 1.06)	**0.09**
2.5 mg	349	27	0.74 (0.45, 1.23)	0.25
5.0 mg	349	24	0.64 (0.38, 1.08)	0.09

Rivaroxaban 2.5 mg vs. Placebo; Stratum 2:

Cumulative MACE prevented, Cumulative TIMI Major Bleeds, Ratio



Rivaroxaban 2.5 mg vs. Placebo; Stratum 2:

Cumulative MACE prevented, Bleeds Req. Med. Attention, Ratio